Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement

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Statistical Analysis Plan

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Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial release	Hongyan Qiao Principal Statistician
2.0	Added details for the Bayesian study design; Incorporated the CIP updates.	Hongyan Qiao, PhD Sr. Principal Statistician Andrew S Mugglin, PhD Paradigm Biostatistics, LLC
3.0	Change the first interim analysis timing to 850 subjects have had the chance to finish 1 year follow up; Delete "the non-parametric Wilcoxon rank-sum test".	Hongyan Qiao, PhD Sr. Principal Statistician Andrew S Mugglin, PhD Paradigm Biostatistics, LLC
4.0	Add clarification for the primary endpoint superiority testing order; Add Section 6.9 Multiplicity Considerations; Rename "additional outcome measures" to "secondary effectiveness endpoints".	Hongyan Qiao, PhD Sr. Principal Statistician

2. Introduction

This Statistical Analysis Plan has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. This Statistical Analysis Plan (SAP) is developed based on the Transcatheter Aortic Valve Replacement (TAVR) Low Risk Clinical Investigational Plan (CIP).

The purpose of this trial is to evaluate the safety and effectiveness of transcatheter aortic valve replacement (TAVR) in the treatment of symptomatic severe aortic stenosis (AS) in subjects who are determined by the Heart Team to be at low surgical risk. The Low Risk trial is a multicenter, prospective, 1:1 randomized study designed to demonstrate non-inferiority (within an absolute margin of 6%) of TAVR to SAVR, as measured by a composite of all-cause death or disabling stroke rate at 24 months. The planned sample size is 1200 subjects who undergo an attempted study procedure, and the statistical methods are Bayesian. Study success will be evaluated according to an analysis plan that includes two possible interim analyses, as well as a final analysis. The first interim analysis is timed when 850 subjects have had the chance to be followed for 12 months (12 months after the 850th procedure date); a second interim analysis is timed when 1200 subjects have had the chance to be followed for 12 months (12 months after the 1200th procedure date); and the final analysis is timed when all subjects have had the chance to be followed for 24 months (24 months after the last LTI subject's procedure date).

A study report will be prepared for submission to US Food and Drug Administration (FDA) at the time study success criteria have been met, for the purpose of seeking market approval. After all subjects have completed all protocol-specified follow-up, a final clinical report including updated long-term safety data will be prepared and submitted.

Any deviations from the Statistical Analysis Plan will be described and justified in the Final Report, as appropriate.

3. Study Objectives

The primary objective of the trial is to demonstrate that the safety and effectiveness of the Medtronic TAVR system, as measured by the rate of all-cause mortality or disabling stroke at 2 years, is non-inferior to SAVR in the treatment of severe aortic stenosis in subjects who have a low predicted risk of mortality at 30 days for SAVR. The following endpoints will be used to evaluate the primary trial objectives:

3.1. Primary Safety and Effectiveness Endpoint

The rate of all-cause mortality or disabling stroke at 2 years

3.2. Secondary Safety Endpoints

- The rate of the composite of death, disabling stroke, life-threatening bleed, major vascular complication, or AKI (II or III) at 30 days
- The rate of new permanent pacemaker implantation at 30 days
- The rate of prosthetic valve endocarditis at one year
- The rate of prosthetic valve thrombosis at one year
- The rate of all stroke (disabling and non-disabling) at one year
- The rate of life-threatening bleeding at one year
- The rate of valve-related dysfunction requiring repeat procedure at one year

3.3. Secondary Effectiveness Endpoints

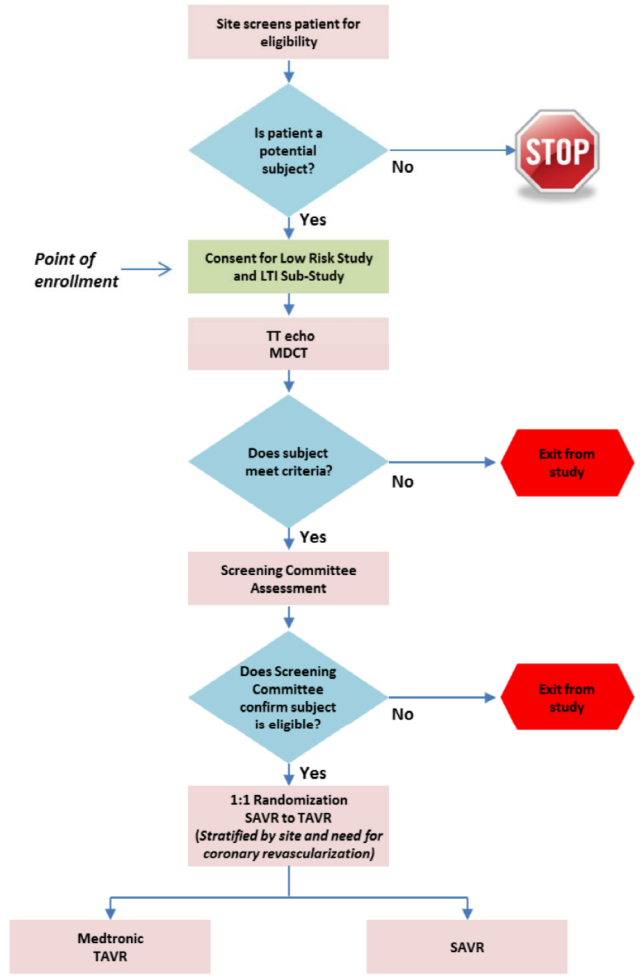
- The rate of valve-related dysfunction, defined as moderate or severe prosthetic valve stenosis, or moderate or severe prosthetic regurgitation at one year (per VARC II)
- Quality of Life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) at 30 days and one year
- The rate of repeat hospitalization for aortic valve disease at one year
- Device Success (VARC II), defined as
  - Absence of procedural mortality, AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND
  - Intended performance of the prosthetic heart valve, defined as the absence of patient-prosthesis-mismatch and mean aortic valve gradient less than 20 mmHg (or peak velocity < 3 m/sec), AND absence of moderate or severe prosthetic valve regurgitation.
- Hemodynamic performance metrics by Doppler echocardiography
  - Mean aortic gradient at one year
  - Effective orifice area at one year
  - Degree of total, peri, and transvalvular prosthetic regurgitation at one year
- New York Heart Association (NYHA) functional classification at one year
- Health-related quality of life at one year as assessed by EQ-5D survey instrument

4. Investigation Plan

No site will implant more than 100 subjects without prior authorization from Medtronic. Subjects who exit from the trial after implantation will not be replaced.

Subjects will be consented for follow-up through ten years. The enrollment period is estimated to be between 18 to 24 months; therefore the estimated total duration of the trial (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be twelve years.

The process of patient screening, subject enrollment, and randomization is as follows:



Notes
1. TTE, MDCT, coronary arteriography, or labs performed for diagnostic purposes prior to consent may be used for the baseline/screening exams, provided they were performed within window and contain the necessary data.
2. Only the sites participating in the LTI Sub-study will consent for both the main study and LTI Sub-study.
3. Subjects who give consent for LTI Sub-study will follow sub-study protocol in addition to main protocol.

5. Determination of Sample Size

5.1. Historical Data

Although the experience with surgical aortic valves in low surgical risk aortic valve replacement populations is extensive, it was not considered possible to leverage much of the data from these studies directly as surgical aortic valve replacement series typically enroll patient populations which include a proportion subjects with a bicuspid or unicuspid valve (excluded from this trial) which may be as high as approximately 50% and also include subjects with purely or primarily regurgitant lesions (also excluded from this trial) whose outcomes may differ from patients with aortic stenosis. As a result, series for which individual patient data were available or which were known to attempt exclusion of patients with bicuspid or unicuspid valves comprise the primary basis for the event rate estimate and additional series were considered only confirmatory in nature. Table 1 presents the rates of all-cause mortality at 24 months from studies which were considered in developing the event rate estimate. The simple weighted average from the studies was 11.4% which was adjusted up to 12% to account for the possibility that surgical candidates at extremely low risk (i.e. the healthiest and youngest potential subjects) may forego randomization into a TAVR trial until longer term data and data from lower surgical risk patients are available for TAVR.

Table 1. Surgical series supporting all-cause mortality event rate estimate

Surgical Series	Number in Cohort	24-Month All-cause Mortality K-M Rate
NOTION SAVR cohort[1]	134	9.8%
3f Pivotal cohort[1]	405	12.7%
Mosaic sub-analysis[2]	646	9.9%
Freestyle sub-analysis[3]	323	13.5%
Simple Weighted Average	1508	11.4%

[1]Entire cohort leveraged (data on file)

[2]Sub-group analysis excluding subjects <65 years of age, with congenital bicuspid valves or with a purely regurgitant lesion

[3]Sub-group analysis excluding subjects <65 years of age, with congenital bicuspid valves, with a purely regurgitant lesion or with the Freestyle valve implanted as a full-root replacement

The 24-month event rate estimate for non-fatal disabling stroke of 3% was generated primarily from the CoreValve US Pivotal High Risk Trial SAVR (3.9%) and TAVR (2.0%) cohorts which used event definitions consistent with this trial.[1] Additional sources of data considered include the NOTION SAVR cohort (4.6%) and the Mosaic and Freestyle cohort sub-analyses (which had rates of 2.0% and 2.3% respectively) all of which collected clinical stroke/cerebrovascular accidents.

The incidence of the primary endpoint of all-cause mortality or disabling stroke at 24 months in each treatment group is expected to be 15%, which is based on an assumed rate of all-cause mortality of 12% at 24 months and a non-fatal disabling stroke rate of 3% at 24 months.

5.2. Sample Size

Although the pre-specified analysis methods are Bayesian, the sample size is guided by a standard frequentist non-inferiority power analysis. Under the assumptions of the 15% incidence in each treatment group, non-inferiority margin δ=0.06, 1:1 randomization, α= 0.05, and power = 85%, the method of Farrington and Manning[2] as implemented in PASS 2013[3] indicates that the required sample size for a single-look analysis is 1032. To allow for up to 6% dropout, 1100 subjects must be accrued. Furthermore, to compensate for power lost in a three-look group

sequential analysis plan using equal information increments and Pocock-type alpha spending, the sample size would have to be increased by about 15%, whereas an O'Brien-Fleming alpha spending approach would increase the total sample size by approximately 1%[4]. The impact of the sampling plan used in this Bayesian design is likely to fall between these two approaches, so an additional 100 subjects (9%) will be accrued, bringing the total estimated sample size to 1200 as treated (AT) subjects, which should provide ample power for establishing non-inferiority in the primary hypothesis test.

6. Statistical Methods

6.1. Randomization

Randomization will follow a 1:1 allocation ratio and be stratified by site and need for revascularization, using a blocked randomization scheme with blocks of randomly varying sizes.

6.2. Analysis Populations

6.2.1. Screening Population

All patients with symptomatic severe AS who provide informed consent will be considered screened and all available data will be entered into the Electronic Data Capture (EDC) system.

6.2.2. Randomized Population

If the subject signs informed consent, meets all inclusion and none of the exclusion criteria, and the Heart Team determines the subject is suitable for randomization in the trial, then the subject is reviewed by the Screening Committee. If the subject is approved by the Screening Committee and the subject is randomized to either TAVR or SAVR, the subject is added to the randomized population. Within the randomized population the following analysis sets are distinguished:

- **The intention to treat (ITT) set:** Subjects are reported according to the randomized assignment, SAVR or TAVR, regardless of what, if any, therapy was actually received. Time zero begins at the date of randomization.
- **The as treated (AT) set:** The AT set consists of all ITT subjects with an attempted implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure (TAVR or SAVR). Time zero begins at the date of the first TAVR or SAVR attempted procedure.
- **The implanted set:** The Implanted set consists of all the AT subjects who are actually implanted with either the Transcatheter Aortic Valve (TAV) or Surgical Aortic Valve (SAV). Time zero begins at the date of the first TAVR or SAVR attempted procedure.
- **The per protocol (PP) set:** The PP set is defined based on the International Council for Harmonisation (ICH) E9 Statistical Principles, which will consist of the following:
    1. All implanted subjects who were implanted according to their randomization; and
    2. Subjects without early exit (eg., lost of follow up) before 24 months (730 days), except those experiencing the primary endpoint (death or disabling stroke) prior to the early exit; and

3. Subjects without crossover to a different type of procedure from their first attempted procedure type before their 24-month visits; and
4. Subjects must satisfy all inclusion/exclusion criteria.

Time zero begins at the date of the first TAVR or SAVR attempted procedure.

The primary analysis for the primary objective, secondary safety objectives, secondary effectiveness objectives (except for valve dysfunction, hemodynamic performance metrics, and device success) will use the AT set. Valve dysfunction, hemodynamic performance metrics, and device success will use the implanted set.

6.3. Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the intention-to-treat (ITT), as treated (AT), and implanted sets. All continuous variables will be summarized as means, medians, standard deviations, interquartile ranges, minima and maxima and will be compared between treatment groups via 95% Bayesian credible intervals (BCIs) for the difference in means. Categorical variables will be summarized as frequencies and percentages and will be compared between treatment groups via 95% Bayesian credible intervals for the difference in proportions.

6.4. Kaplan-Meier Analyses

For safety related endpoints, the Kaplan-Meier event rates at 30 days, 6 months, 12 months, 18 months and annually through 10 years will be provided. For these analyses, these times correspond to 30 days, 183 days, 365 days, 545 days, 730 days, and annually through 10 years (365×3, 365×4, 365×5, etc.). At each time point with data, the product-limit estimate of the event rate, the number of subjects at risk, the number of subjects with events, the Peto standard error of the estimate, and the loglog transformed 95% confidence interval using the Peto standard error will be presented.

For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death in those endpoints where death is not the endpoint).

6.5. Primary Objective

The primary endpoint of all-cause mortality or disabling stroke at 24 months will be evaluated using the absolute difference of the TAVR rate and the SAVR rate for all-cause mortality or disabling stroke during a fixed follow-up of 24 months. The hypothesis test is designed to show non-inferiority of TAVR to SAVR for the primary endpoint.

6.5.1. Hypothesis of non-inferiority

The primary objective is to establish that TAVR is non-inferior to SAVR for the primary endpoint. The hypothesis of interest is:

$$H: \pi_T < \pi_C + \delta$$

where π_T and π_C respectively denote incidence of all-cause mortality or disabling stroke at 24 months for the treatment (TAVR) and control (SAVR) groups, and $\delta = 0.06$. This study is designed using Bayesian statistical techniques. TAVR will be considered to be non-inferior to SAVR if it can be established that the posterior probability $\Pr(H_{\delta=0.06} \mid \text{data}) > \Psi$, where Ψ is a pre-specified threshold value. In addition, the primary endpoint (superiority) will be tested according to the testing order specified in Section 6.9. The values chosen for Ψ and Ψ_{SUP} are chosen to ensure type I error rates are not larger than 0.05 for non-inferiority and 0.025 for superiority.

6.5.2. Analysis Plan

The two interim analyses and final analysis are planned when:

1. 850 subjects have had the chance to be followed for 12 months (12 months after the 850th procedure date);
2. 1200 subjects have had the chance to be followed for 12 months (12 months after the 1200th procedure date);
3. All subjects have had the chance to be followed for 24 months (24 months after the last LTI subject's procedure date).

At the first interim analysis, the posterior probability of non-inferiority $P(H_{\delta=0.06} \mid \text{data})$ will be calculated, and if this probability exceeds a pre-specified threshold Ψ, non-inferiority will be concluded. This will be considered an "early win" for non-inferiority, and a regulatory submission will follow. Otherwise, follow-up will continue until the second interim analysis, where again the posterior probability of non-inferiority $P(H_{\delta=0.06} \mid \text{data})$ will be calculated, and if this probability exceeds a pre-specified threshold Ψ, non-inferiority will be concluded and a regulatory submission will follow. If non-inferiority is not concluded at either of the interim analyses, follow-up will continue until all subjects have had the chance to be followed for 24 months (24 months after the last LTI subject's procedure date), and non-inferiority will be tested a third time. The standard for concluding non-inferiority in each case is the same: $P(H_{\delta=0.06} \mid \text{data}) > \Psi$.

If non-inferiority is established at either interim analysis, a test of superiority may be performed (See Section 6.9 for additional requirements and testing sequence). If $P(H_{\delta=0} \mid \text{data}) > \Psi_{SUP}$, superiority will be established at this time. However, if $P(H_{\delta=0} \mid \text{data}) \leq \Psi_{SUP}$, subjects will continue to be followed until the full cohort has had the chance to be followed for 24 months (24 months after the last LTI subject's procedure date), at which time a delayed determination of superiority may be made if $P(H_{\delta=0} \mid \text{data}) > \Psi_{SUP}$.

If non-inferiority is not established until the final analysis, then superiority will only be tested at that time per the testing sequence outlined in Section 6.9.

The maximum number of non-inferiority assessments is three (first interim analysis, second interim analysis, final analysis). The maximum number of superiority assessments is two (simultaneous to passing the non-inferiority assessment for the primary endpoint and the hierarchical testing for the secondary endpoints listed in Section 6.9, or at the final analysis in the event that superiority is not established at one of the interim analyses).

The statistical approach for these analyses is Bayesian. The prior distributions for π_T and π_C in these calculations are Beta(1,1). In each analysis (interim or final), any subject with missing 24-month outcome will have that outcome predicted via a Bayesian piecewise exponential survival model that incorporates follow-up to date. Within a treatment group, let a subject's time to event follow a piecewise exponential model whose hazard function $\lambda(\tau)$ is piecewise constant over the 3 partitioning intervals defined by the cutoff points 0, 30 days, 183 days, and 730 days. The parameters for each of the 3 intervals are assigned diffuse Gamma prior distributions, with mean 1 and variance 100, which at the time of analysis are updated based on observed data, and unobserved 24-month outcomes are predicted with probabilities determined by this model. Combining predicted and observed 24-month outcomes and integrating out the predictive distributions results in a posterior probability of non-inferiority (or superiority) that accounts for missing data as well as the uncertainty in the prediction, and this is the quantity that is compared to Ψ (or Ψ_{SUP}) to assess non-inferiority (or superiority). This approach is similar to that taken in the SURTAVI trial[5], though in this case the statistical model underlying the predictions is based on a time-to-event model rather than a set of beta-binomial models. It is also similar to the approach taken in Wilber et al[6]. The thresholds Ψ and Ψ_{SUP} are selected empirically to achieve a type I error rate (under extensive simulation) of at most 0.05 for non-inferiority testing and at most 0.025 for superiority testing.

6.5.3. Note on Timing of Stroke Determination

It may take up to 90 days after a stroke is reported to determine whether it is a disabling stroke. In such cases, the date of the stroke is the date of occurrence and not the date of determination. Furthermore, when the database is locked for interim and final analyses, it is possible that some strokes will still be waiting for the 90-day MRS. In such cases,

the CEC will make their adjudications based on all available data, and the analysis will be based on the CEC adjudicated results.

6.6. Description of Performed Analysis, per Population

The primary analysis for the primary endpoint will be performed on the AT set. In addition, it will also be performed on the ITT, Implanted, and PP sets. The inferential statistics for the following secondary endpoints will be performed on the AT set:

- The rate of the composite of death, disabling stroke, life-threatening bleed, major vascular complications, or AKI (II or III) at 30 days
- The rate of new permanent pacemaker implantation at 30 days
- The rate of prosthetic valve endocarditis at one year
- The rate of prosthetic valve thrombosis at one year
- The rate of all stroke (disabling and non-disabling) at one year
- The rate of life-threatening bleeding at one year
- The rate of valve-related dysfunction requiring repeat procedure at one year
- Quality of Life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year
- The rate of repeat hospitalization for aortic valve disease at one year
- New York Heart Association (NYHA) functional classification at 30 days, 6 months, one year, 18 months, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years
- Health-related quality of life at one year as assessed by EQ-5D survey instrument

The implanted set will be used for analyzing the primary endpoint, secondary endpoint of prosthetic valve dysfunction, device success, and echocardiographic assessment of valve performance.

6.7. Secondary Safety Endpoints

The following secondary endpoints will be compared between TAVR and SAVR subject cohorts using the appropriate Bayesian version of analysis for comparing proportions. In addition, Kaplan-Meier estimates will be provided.

- The rate of the composite of death, disabling stroke, life-threatening bleed, major vascular complications, or AKI (II or III) at 30 days
- The rate of new permanent pacemaker implantation at 30 days
- The rate of prosthetic valve endocarditis at one year
- The rate of prosthetic valve thrombosis at one year
- The rate of all stroke (disabling and non-disabling) at one year
- The rate of life-threatening bleeding at one year
- The rate of valve-related dysfunction requiring repeat procedure at one year

6.8. Secondary Effectiveness Endpoints

- The rate of valve-related dysfunction, defined as moderate or severe prosthetic valve stenosis, or moderate or severe prosthetic regurgitation at one year (per VARC II)

  The incidence estimate will be provided for the two treatment groups at the specified time point. The statistical method will be the Bayesian version of a comparison of proportions. The incidence estimates will also be reported at the following time points: 30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years.

PROSTHETIC VALVE DYSFUNCTION	
Stenosis: moderate/severe	Any of the following 1) Peak aortic velocity >4 m/s OR mean aortic gradient >40 mmHg, AND EOA <0.8 cm^2. 2) Peak aortic velocity >4 m/s OR mean aortic gradient >40 mmHg, AND EOA ≥0.8 cm^2, and DVI <0.25, 3) Peak aortic velocity ≤4 m/s and mean aortic gradient ≤ 40 mmHg, AND EOA <0.8 cm^2, and DVI <0.25
Paravalvular regurgitation	Moderate/ Severe paravalvular regurgitation
Transvalvular regurgitation	Moderate/ Severe transvalvular regurgitation
Total regurgitation	Moderate/ Severe total regurgitation

Notes:
1. DVI = Doppler Velocity Index (LVOT VTI/valve VTI)
2. For subjects with BSA <1.6 m^2, the EOA criteria for significant (moderate or severe) stenosis is <0.6 cm^2
3. For subjects with LVOT diameter >2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is <0.2 cm^2
4. Reporting of prosthetic valve dysfunction will be based on core lab results.
5. Prosthetic valve dysfunction events are not reported as adverse events, unless the dysfunction is accompanied with clinical sequelae at the time of event detection, and the clinical sequelae are chronologically and physiologically associated with the dysfunction. However, prosthetic dysfunctions that are associated with adverse events, and that meet the definition of a serious adverse event, should be reported as such.

- Quality of Life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) at 30 days and one year

  The endpoint will be evaluated using a Bayesian analog of a two-sample t-test. Descriptive statistics for KCCQ change from baseline will also be reported at 30 days, 6 months, one year, and annually through 5 years.

- The rate of repeat hospitalization for aortic valve disease at one year.

  The incidence estimate will be provided for the two treatment groups at the specified time point. The statistical method will be the Bayesian version of analysis for comparing proportions. In addition, the Kaplan-Meier estimates will be provided at the following time points: 30 days, 6 months, 12 months, 18 months, and annually thereafter through 10 years.

- Device Success (VARC II), defined as
  - Absence of procedural mortality, AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND
  - Intended performance of the prosthetic heart valve, defined as the absence of patient-prosthesis-mismatch and mean aortic valve gradient less than 20 mmHg (or peak velocity < 3 m/sec), AND absence of moderate or severe prosthetic valve regurgitation.

  The incidence estimate will be provided for the TAVR group.

  The criteria for ECHO will be based on the ECHO Core Lab Data:

  - Absence of patient-prosthesis-mismatch
    1. For subjects with BMI < 30 kg/m^2, index effective orifice area (EOAi) > 0.85 cm^2/m^2
    2. For subjects with BMI ≥ 30 kg/m^2, index effective orifice area (EOAi) > 0.70 cm^2/m^2
    3. BMI = weight(kg)/(height (m)) ^{2}

- Mean aortic gradient < 20 mmHg or peak velocity < 3 m/sec;
- Absence of moderate or severe prosthetic valve regurgitation. Total Aortic Prosthetic Regurgitation on the ECHO CORE LAB form not equal to moderate or severe.

All of the above components must be satisfied to count as a device success. If any of the above components fails, the endpoint will be counted as a failure.

For the overall device success rate, the numerator will be the number of subjects whose procedures result in device success as described above, and the denominator will be the number of subjects whose device success results are not missing (either success or failure). Note that this analysis excludes those subjects with a missing response to any of the above five components (eg, the field "Post-implant Severity of Total Aortic Regurgitation"="Unable to Assess" or "Not Recorded", missing mean aortic gradient, or missing peak velocity, etc.) and without a "NO" response to any of the components.

- Hemodynamic performance metrics by Doppler echocardiography
  - Mean aortic gradient at one year
  - Effective orifice area at one year
  - Degree of total, peri, and transvalvular prosthetic regurgitation at one year

  For mean gradient and effective orifice area, the descriptive statistics will be reported at each of the assessed time point (30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years). The statistical method will be the Bayesian version of a two-sample t-test.

  Prosthetic regurgitation severity will be reported as proportions at each of the assessed time point (30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years). The statistical method will be the Bayesian version of a comparison of proportions.

- New York Heart Association (NYHA) functional classification at one year

  NYHA function classification will be reported as proportions at each of the assessed time point (30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years). The statistical method will be the Bayesian version of a comparison of proportions.

- Health-related quality of life as assessed by EQ-5D survey instrument at one year.

  The endpoint will be evaluated using a Bayesian analog of a two-sample t-test.

6.9. Multiplicity Considerations

It is recognized that with a multiplicity of tests comes an inflation in the chance of a false finding of superiority or non-inferiority. Therefore, for the purpose of seeking approved labeling claims on designated secondary objectives, the following standard will be used: if the primary objective demonstrates non-inferiority, claims will be sought for selected secondary non-inferiority and superiority objectives and for superiority on the primary objective metric. These will be tested via a hierarchical (sequential) testing order that preserves the overall study-wise type I error rate at the level of 0.05. The testing order is specified below. The following secondary objectives are tested in order, and testing continues if and only if all previous objectives have met their designated success criterion.

1. Transvalvular mean gradient at 1 year (non-inferiority)
2. Effective orifice area at 1 year (non-inferiority)
3. Change in NYHA classification from baseline to 1 year (non-inferiority)
4. Change in KCCQ score from baseline to 1 year (non-inferiority)
5. Transvalvular mean gradient at 1 year (superiority)
6. Effective orifice area at 1 year (superiority)
7. Change in KCCQ score from baseline to 30 days (superiority)

All of the above non-inferiority will be tested with a type I error standard of 0.05 and superiority tests will be tested with a type I error standard of 0.025. If all of the above tests meet their success criterion, the primary endpoint (superiority) will be tested using a type I error rate of 0.025.

For the purposes of seeking claims, these objectives will only be evaluated once, at the same time as non-inferiority of the primary objective is established. The only exception to this is the primary endpoint superiority test, which carries the possibility of a delayed determination of superiority and may thus meet its success criterion at a different time (see Section 6.5.2).

The remaining secondary endpoints (see Section 3.2 and Section 3.3) may be of interest for scientific reasons but will not be the basis for supporting labeling claims; they are thus outside of the hierarchical testing procedure. Similarly, for those objectives that test non-inferiority, if non-inferiority is established, a test of superiority may also be conducted, but unless specifically itemized in the list, such superiority testing is not part of the hierarchical testing procedure; these superiority tests may be of interest for scientific reasons but will not be the basis for supporting labeling claims.

6.9.1. Ordered List of Secondary Objectives to be Tested to Support Labeling Claims

1. Transvalvular mean gradient at 1 year (non-inferiority). The hypothesis of interest is

$$H: \mu_{TAVR} < \mu_{SAVR} + 5$$

where μ_{TAVR} and μ_{SAVR} denote the average mean gradient at 1 year, measured in mmHg. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

Rationale for Delta: A difference less than 5 mmHg for mean gradient is not considered clinically relevant for the TAVR Low Risk Executive Committee.

2. Effective orifice area at 1 year (non-inferiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR} - 0.1$$

where μ_{TAVR} and μ_{SAVR} denote the mean effective orifice area at 1 year, measured in cm^2. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

Rationale for Delta: A difference less than 0.1 cm^2 for effective orifice area is not considered clinically relevant for the TAVR Low Risk Executive Committee.

3. Change in NYHA classification from baseline to 1 year (non-inferiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR} - 0.375$$

where μ_{TAVR} and μ_{SAVR} denote the mean number of classification improvements in NYHA from baseline to 1 year. For subjects with NYHA categories at both baseline and 1-year visit, the NYHA classification improvements will be calculated as $NYHA_{baseline} - NYHA_{12month}$. The objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

Rationale for Delta: A difference less than 0.375 for NYHA classification is not considered clinically relevant for the TAVR Low Risk Executive Committee.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 1 year (non-inferiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR} - 5$$

where μ_{TAVR} and μ_{SAVR} denote the mean changes in the KCCQ score from baseline to 1 year. For subjects with KCCQ score at both baseline and 1 year, the change in KCCQ will be calculated as $KCCQ_{1year} - KCCQ_{baseline}$. The objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

Rationale for Delta: A 5-point improvement or decrease in KCCQ is the minimum difference that is clinically relevant.[7]

5. Transvalvular mean gradient at 1 year (superiority). The hypothesis of interest is

$$H: \mu_{TAVR} < \mu_{SAVR}$$

where μ_{TAVR} and μ_{SAVR} denote the average mean gradient at 1 year, measured in mmHg. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.975.

6. Effective orifice area at 1 year (superiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR}$$

where μ_{TAVR} and μ_{SAVR} denote the mean effective orifice area at 1 year, measured in cm^2. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.975.

7. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 30 days (superiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR}$$

where μ_{TAVR} and μ_{SAVR} denote the mean changes in the KCCQ score from baseline to 30 days. For subjects with KCCQ score at both baseline and 30 days, the change in KCCQ will be calculated as $KCCQ_{30day} - KCCQ_{baseline}$. The objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.975.

6.10. Heterogeneity/Poolability

Incidence of the primary endpoint will be evaluated for poolability across key subgroups. In particular, the primary endpoint will be examined for differences in outcome between gender, and need for revascularization. Tests for these outcomes will be performed to evaluate potential interactions between treatment and gender, and between treatment and need for revascularization.

6.10.1. Geography Poolability Analysis

Poolability analyses may be conducted either with frequentist or Bayesian statistical methods. The analysis descriptions below are written with the language of frequentist methods. If Bayesian methods are used, analogous models will be employed, with non-informative prior distributions, and statements below such as "significant at the 0.15 level" can be understood to mean if the 85% equal-tailed Bayesian credible interval (BCI) for the parameter of interest excludes 0.

6.10.1.1. Primary Endpoint by Geography

The interaction between geography (US vs. Other) and treatment on the probability of death or disabling stroke at 24 months will be compared using a Cox proportional hazard model. This analysis will be performed on the AT set. If the resulting test is significant at the 0.15 level, further exploratory analysis will attempt to identify covariates that may explain treatment effect differences between the regions. Otherwise, the data will be considered to be poolable across geographies.

6.10.1.2. Univariate Covariate Analysis

If in the analysis of primary endpoint by geography, the resulting p-value is ≤ 0.15, then the following baseline characteristics will be examined individually as potential predictors of death or disabling stroke:

- Gender

- Age
- Baseline NYHA
- STS score
- Baseline LVEF
- Hypertension
- Diabetes
- Coronary artery disease
- Prior stroke
- Prior MI
- Prior PCI

6.10.1.3. Multivariable Analysis

Along with geography and treatment-by-geography interaction, any covariates with a 0.20 significance level from the Univariate Covariate Analysis will be included in a Cox proportional hazard model. If this multivariable regression does not result in a significant (level 0.15) geography by treatment interaction after adjustment for these baseline factors, then outcome results will again be considered poolable across geographies. If geography by treatment interaction is still significant (level 0.15) after adjustment for these factors, results will be presented by geography and the clinical significance of these differences will be assessed.

6.10.2. Site Poolability Analysis

If the geographic regions are considered to be poolable, then the Site Poolability Analysis will be performed on all sites, regardless of geography; the geographic regions (US vs. Other) will not be taken into account.

Should, however, the geographic regions US and Other not be considered to be poolable, then for both of these regions a separate site poolability analysis will take place.

6.10.2.1. Pooling of Small Sites

Sites should contribute at least 5 treatment and at least 5 control subjects to the AT set. If this is not the case, the site is considered a “small site”; small sites will be ordered by the date of first procedure in the AT set. Starting with the first “small site”, a pseudo-site will be created by adding subjects from successive “small sites”. Once the number of subjects (treatment and control subject together) reaches or exceeds the size of the median enrollment (treatment and control subject together) of the “large sites”, then a second pseudo-site will be created, beginning with the next site not already included in the first pseudo-site. Additional pseudo-sites, if needed, would be created in the same manner.

If the geographic regions (US vs. Other) are considered to be poolable then the pseudo-sites can consist of small sites of both geographic regions. If however the regions are not considered to be poolable, then specific pseudo-sites for both regions need to be created. A separate site poolability analysis will be performed for both regions.

6.10.2.2. Primary Endpoint by Site

The interaction between site or pseudo-site and treatment on the probability of death or disabling stroke will be compared using a Cox proportional hazard model. This analysis will be performed in the AT set. If the resulting test is significant at the 0.15 level, further exploratory analysis will be conducted. One analysis will implement a random-effects model for the primary endpoint that includes site as a random effect. Another analysis will attempt to identify covariates that may explain treatment effect differences among the sites. Otherwise, the data will be considered to be poolable across study sites.

6.10.2.3. Multivariable Analysis

If in the analysis for Primary Endpoint by Site, the resulting test is significant at the 0.15 level, then the covariates significant at the 0.20 level from Univariate Covariate Analysis (6.10.1.2) will be included along with site in a Cox proportional hazard model. If this multivariable regression does not result in a significant (level 0.15) site by treatment interaction after adjustment for these baseline factors, then outcome results will again be considered poolable across study sites. If site by treatment interaction is still significant (level 0.15) after adjustment for these factors, results will be presented by site and the clinical significance of these differences will be assessed.

7. Additional Analysis

There will be approximately 50 AT subjects from Japan in this study. Once the primary objective demonstrates non-inferiority (either at one of the interim analyses, or at the final analysis), an additional report specifically for these Japanese subjects will be prepared as requested by PMDA, which includes descriptive statistics for the primary endpoint and all secondary endpoints. In addition, poolability analysis (Japan vs. non-Japan data) will be performed.

8. Validation Requirements

Statistical programming for the analysis datasets, primary endpoint, secondary safety endpoints, and secondary effectiveness endpoints require Level 1 (independent) validation. Other objectives and sub-group analyses require Level 1 (independent) or Level 2 (Peer review) validation.

9. References

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